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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,683	10/02/2003	David Borcherding	USA3960 US CNT	8394

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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
05/25/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/677,683	BORCHERDING ET AL.	
	Examiner	Art Unit	
	/Mark L. Berch/	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04/20/2007* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-10,12-16,18,19,21-35,48 and 49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-16,18,19,21-35,48 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/998,976* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Information Disclosure Statement

The Andriko reference has been crossed out. It did not identify the article by volume, page number and date. Hence it is not a proper citation, and is not of record. The reference however was considered in full.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 is rejected under 35 U.S.C. 112, paragraphs 1 and 2, as the claimed invention is not described, or is not described in such full, clear, and exact terms as to enable any person skilled in the art to make and use the same, and/or failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention. Specifically:

The new wording of "lymphoid tissue type, folicullar reticulum, cell sarcoma" is problematic: What is it? Applicants have inserted two commas, and now state that, despite the commas, that this is one thing, that the "folicullar reticulum" is an "interjected adjectival expression", whatever that means. Applicants were asked previously what this is, and applicants do refer to their "intended meaning" without stating just what that

"intended meaning" actually is. According to the preamble of the claim, "lymphoid tissue type, folicullar reticulum, cell sarcoma" is a type of Neoplastic disease. The examiner cannot locate any reference to a disease with this specific name.

Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The scope of "autoimmune disease" is unclear. Consider Primary sclerosing cholangitis (PSC), Multiple Sclerosis, scleroderma, Phacogenic Uveitis, fibromyalgia, Bullous pemphigoid, Polymyositis, Rosacea, Hidradenitis suppurativa, Multifocal Motor Neuropathy with conduction block (MMN) and Still's disease. Whether these are or are not autoimmune disorders is not known, and indeed determining what is and what is not an autoimmune disorder has proved in numerous cases to be very troublesome. For example, there is a substantial scientific debate over whether MS is or is not an autoimmune disorder. Hence, it is not known whether these diseases do or do not fall within the claim, rendering the claim indefinite.

The traverse is unpersuasive, and indeed, appears to miss the point. Applicants state, "Whether listed diseases are considered by the Examiner to be auto-immune is irrelevant". The examiner is not referring to whether the examiner considers them to be autoimmune, but rather to the fact that there is no agreement on this. Applicants continue, "The diseases are not changed by the categorization." Of course, not, but whether the disease does or does not fall within the scope of the claim very much depends on whether the disese does or does not fall into the category of "autoimmune" Applicants also state they

the are allowed "to be their own lexicographers." Applicants can indeed, set forth specialized definitions of terms. The specification, however, has not done this.

Claims 3-10, 12-19, 21, and 49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Generally speaking, these claims fall into four categories:

I. Treatment of cancers, which are hyperproliferative disorders: Claims 4-10

II. Treatment of other, non-cancerous hyperproliferative disorders: Claims 12-14

III. Treatment of both: Claim 3

IV. Prevention of apoptosis: Claims 15-16, 18-19, and 21. Claim 21 does not actually mention apoptosis, but judging from the specification, this protection arises from the prevention of apoptosis.

The treatment of cancers generally, and hyperproliferative disorders generally cannot possibly be considered enabled. Nor can the prevention of apoptosis. The examiner notes for the record that these are opposing utilities. That is, apoptosis (programmed cell death) is the body's most powerful anti-tumor mechanism. Suppression of apoptosis means suppression of the body's anti-cancer regime. Important anti-cancer drugs such as paclitaxel and tamoxifen operate by inducing apoptosis. The examiner knows of no anti-cancer drug which operates by suppressing apoptosis; such a mechanism would make no sense. Indeed, it is becoming increasingly clear that the most important determinant of

tumor resistance may be a generalized resistance to induction of apoptosis. That is, tumor cells manage to survive because they are resistant to the body's apoptosis mechanisms. Drugs that suppress apoptosis would be expected make cancer worse.

Applicants state that they agree that "apoptosis and hyperproliferation are opposite" but say that they are similar in that they "share a similarity of requiring a degree of cell cycling." The examiner does not see much of a similarity. But even if true, it does not at all get to the essential problem here, which is that an agent which suppresses apoptosis would be reasonably expected to make cancer worse, not better.

Similarly, some important autoimmune disorders such as lupus and MS (if that is an autoimmune disease) and Sjögren's syndrome are characterized by too little apoptosis, and so agents which further suppress apoptosis would be expected to make matters worse.

By way of background, four cases are of particular relevance to the question of enablement of a method of treating cancers broadly or even generally:

In *In re Buting*, 57 CCPA 777, 418 F.2d 540, 163 USPQ 689, the claim was drawn to "The method of treating a malignant condition selected from the group consisting of leukemias, sarcomas, adenocarcinomas, lymphosarcomas, melanomas, myelomas, and ascitic tumors" using a small genus of compounds. The Court decided that humans testing "limited to one compound and two types of cancer" was not "commensurate with the broad scope of utility asserted and claimed".

In *Ex parte Jovanovics*, 211 USPQ 907 the claims were drawn to "the treatment of certain specified cancers in humans" by the use of a genus of exactly two compounds, the N-formyl or N-desmethyl derivative of leurosine. Applicants submitted "affidavits, publications and data" for one of the compounds, and a dependent claim drawn to the use of

that species was allowed. For the other, no data was presented, applicants said only that the other derivative would be expected to be less effective; claims to the genus were refused.

In *Ex parte Busse*, et al., 1 USPQ2d 1908, claims were drawn to A therapeutic method for reducing metastasis and neoplastic growth in a mammal" using a single species. The decision notes that such utility "is no longer considered to be "incredible", but that "the utility in question is sufficiently unusual to justify the examiner's requirement for substantiating evidence. Note also that there is also a dependent claim 5 which specified "wherein metastasis and neoplastic growth is adenocarcinoma, squamous cell carcinoma, melanoma, cell small lung or glioma." The decision notes that "even within the specific group recited in claim 5 some of the individual terms used actually encompass a relatively broad class of specific types of cancer, which specific types are known to respond quite differently to various modes of therapy."

In *Ex parte Stevens*, 16 USPQ2d 1379 a claim to " A method for therapeutic or prophylactic treatment of cancer in mammalian hosts" was refused because there was "no actual evidence of the effectiveness of the claimed composition and process in achieving that utility."

In response applicants, state, "However, case law relates to law not to science". This is true but not the point. These cases reflect the legal treatment of claims drawn to the treatment of cancer broadly, and the examiner will be guided by them. Thus, while applicants state that these cases "cannot be properly relied upon for teachings of the skills in the art ...To the extent that outdated teachings of the level of skill in the art....", applicants have not identified any "outdated teachings" being relied on.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Due to the deeply nested nature of the Ra variable (Ra can be NR1R3, where R1 can be a choice with Q and two W groups, and Q can have another R3 substituent, and W can be assorted rings with B (which has the R6 substituent) and several X substituents, which X substituents can have R4 and R5 substituents on them, variables which have very broad definitions), the claim covers millions if not billions of compounds.

The traverse on this point is not persuasive. Applicants previously stated, "Numbers alone ... by themselves ... are not indicative of undue experimentation." The examiner is not saying that any factor "alone" is indicative of undue experimentation. The staggeringly large size of the genus must be a factor in the direction of lack of enablement. Applicants point to the species listed in Table 1, but this in no way limits the scope of the claims.

Applicants state, "The ---Z-Ra portion is crafted to reduce basicity of the nitrogen to which the portion is attached. Although the number of radicals that achieve this result is

large, as a group they achieve the identical result." The examiner agrees with the first sentence but not the second. The ---Z-Ra portion does more than that. It also affects the size, shape and electronic distribution of the molecule. And indeed, applicants seem to argue against the notion that these ZRa groups achieve an "identical result."

Applicants state, "The –Z-Ra portion of the molecule is not responsible for binding the CDK." Applicants go on to explain that this part of the molecule affect the degree to which there is "uptake of the compound by red blood cells", and applicants explain which this is very important, that "when the compound is sequestered within a red blood cell the compound cannot freely pass from the plasma to target tissues." The examiner agrees that the test measures the distribution ratio of the tested compound between the red blood cells and plasma. How is this an argument for enablement? This is basically an argument for the fact that –Z-Ra portion of the molecule is not irrelevant, but plays an essential role in making sure that the molecule as a whole can get to where it is needed. It does show that for some compounds, the ration is unfortunately rather high. The examiner's assumption was that all parts of the molecule are important.

(b) Scope of the diseases covered. The coverage is immense. There are hundreds of types of cancers and tumors. They can occur in pretty much every part of the body. Here are some assorted categories:

A. CNS cancers cover a very diverse range of cancers in many categories and subcategories. There are an immense range of neuroepithelial tumors. Gliomas, the most common subtype of primary brain tumors, most of which are aggressive, highly invasive, and neurologically destructive tumors are considered to be among the deadliest of human cancers. These are any cancers which show evidence (histological, immunohistochemical, ultrastructural) of

glial differentiation These fall mostly into five categories. There are the astrocytic tumors (Astrocytomas): Pilocytic astrocytoma (including juvenile pilocytic astrocytoma, JPA, and pediatric Optic Nerve Glioma) Diffuse astrocytomas (including Fibrillary astrocytomas, Protoplasmic astrocytomas and Gemistocytic astrocytomas), Anaplastic astrocytomas (including adult Optic Nerve Glioma), Glioblastoma multiforme (GBM), gliosarcoma and giant cell glioblastoma, and Pleomorphic xanthoastrocytoma. GBM exists in two forms, primary and secondary, which have very different clinical histories and different genetics, but GBM is considered to be one clinical entity. Second, there are the oligodendroglial tumors (Oligodendrogliomas): Low grade Oligodendroglioma and Anaplastic Oligodendroglioma. Third, there is oligoastrocytomas ("mixed glioma"), a type of tumor with both astrocytoma & oligodendroglioma features. The fourth type is the Ependymomas, which are intracranial gliomas, including Papillary Ependymoma, Myxopapillary ependymoma, tanycytic ependymoma, Anaplastic ependymoma and subependymal giant-cell astrocytomas. A fifth type is the Gangliogliomas (glioneuronal tumors or glioneurocytic tumors), which have both glial and neuronal components, and are extremely varied, based in part on what types of glial and what types of neuronal components are present. These include Papillary Glioneuronal Tumor (PGNT), a range of Supratentorial gangliogliomas, assorted intramedullary spinal cord gangliogliomas, Pineal ganglioglioma, Hypothalamic ganglioglioma, cerebellar ganglioglioma, Ganglioglioma of the right optic tract, rosetted glioneuronal tumor ("glioneurocytic tumor with neuropil rosettes"), composite pleomorphic xanthoastrocytoma (PXA)-ganglioglioma, desmoplastic ganglioglioma (both infantile (DIG) and non- infantile), Angioganglioglioma, and others. There are also some Glial tumors which do not comfortably fit into these five categories, notably Astroblastoma, Gliomatosis

cerebri, and chordoid glioma, which is found solely in the Hypothalamus and Anterior Third Ventricle. Other neuroepithelial tumors include astrocytic tumors (e.g. astrocytomas) oligodendroglial tumors, Ependymal cell tumors (e.g. myxopapillary ependymoma), mixed gliomas (e.g. mixed oligoastrocytoma and ependymo-astrocytomas) tumors of the choroid plexus(Choroid plexus papilloma, Choroid plexus carcinoma), assorted neuronal and Neuroblastic tumors (e.g. gangliocytoma, central neurocytoma, dysembryoplastic neuroepithelial tumor, esthesioneuroblastoma, Olfactory neuroblastoma, Olfactory neuroepithelioma, and Neuroblastomas of the adrenal gland), pineal parenchyma tumors (e.g. pineocytoma, pineoblastoma, and Pineal parenchymal tumor of intermediate differentiation), embryonal tumors (e.g. medulloepithelioma, neuroblastoma, retinoblastoma, ependymoblastoma, Atypical teratoid/rhabdoid tumor, Desmoplastic medulloblastoma, Large cell medulloblastoma, Medullomyoblastoma, and Melanotic medulloblastoma) and others such as polar spongioblastoma and Gliomatosis cerebri. A second Division is tumors of the meninges. This includes tumors of the meningothelial cells, including Meningiomas (Meningothelial, Fibrous (fibroblastic), Transitional (mixed), Psammomatous, Angiomatous, Microcystic, Secretory, Lymphoplasmacyte-rich, Metaplastic, Clear cell, Chordoid, Atypical, Papillary, Rhabdoid, Anaplastic meningioma) and the non- Meningioma tumors of the meningothelial cells (Malignant fibrous histiocytoma, Leiomyoma, Leiomyosarcoma, Rhabdomyoma, Rhabdomyosarcoma, Chondroma, Chondrosarcoma, Osteoma, Osteosarcoma, Osteochondroma, Haemangioma, Epithelioid haemangioendothelioma, Haemangiopericytoma, Angiosarcoma, Kaposi sarcoma). There are also Mesenchymal, non-meningothelial tumors (Lipomas, Angiolipoma, Hibernoma Liposarcoma, (intracranial)Solitary fibrous tumor, and Fibrosarcoma) as well

as Primary melanocytic lesions (Diffuse melanocytosis, Melanocytoma, Malignant melanoma, and Meningeal melanomatosis). A third Division are the tumors of Cranial and Spinal Nerves. This includes Cellular schwannomas, Plexiform schwannomas and the Melanotic schwannomas (e.g. psammomatous melanotic schwannoma , Neuro-axial melanotic schwannoma, Dorsal dumb-bell melanotic schwannoma). There is also neurofibroma, Perineurioma (Intraneural and Soft tissue) and malignant peripheral nerve sheath tumor (MPNST), including Epithelioid, MPNST with divergent mesenchymal differentiation, and MPNST with epithelial differentiation. A fourth division are Germ Cell Tumors, including germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma (Mature teratoma, Immature teratoma, and Teratoma with malignant transformation). A fifth division are the tumors of the Sellar Region, viz. pituitary adenoma, pituitary carcinoma, granular cell myoblastoma and craniopharyngiomas (Adamantinomatous and Papillary). Yet another division are local extensions from regional tumors, including paraganglioma, chodroma, chordoma, and chondrosarcoma. There are also Primitive Neuroectodermal Tumors (PNETs) including Medulloblastomas, medulloepitheliomas, ependymoblastomas and polar spongioblastomas. There are Vascular brain Tumors e.g. the hemangioblastomas, there is CNS Lymphoma (which can be primary or secondary) and Meningeal Carcinomatosis. There are Lymphoma AND Haemopoietic neoplasms including Malignant lymphomas (which can be primary or secondary), Plasmacytoma, and Granulocytic sarcoma. And there are many, many others.

B. Leukemia is any malignant neoplasm of the blood-forming tissues. Leukemia can arise from many different sources. These includes viruses such as EBV, which causes Burkitt's lymphoma, and HTLV-1, linked to certain T cell leukemias. Others are linked to genetic

disorders, such as Fanconi's anemia, which is a familial disorder, and Down's Syndrome. Other leukemias are caused by exposure to carcinogens such as benzene, and some are actually caused by treatment with other neoplastic agents. Still other leukemias arise from ionizing radiation, and many are idiopathic. Leukemias also differ greatly in the morphology, degree of differentiation, body location (e.g. bone marrow, lymphoid organs, etc.) There are dozens of leukemias. There are B-Cell Neoplasms such as B-cell prolymphocytic leukemia and Hairy cell leukemia (HCL, a chronic leukemia). There are T-Cell Neoplasms such as T-cell prolymphocytic leukemia, aggressive NK cell leukemia, adult T cell leukemia/lymphoma (ATLL), and T-cell granular Lymphocytic leukemia. There are different kinds of acute myeloid leukemias, acute promyelocytic leukemias, acute myelomonocytic leukemia, chronic myelomonocytic leukemia, acute monocytic leukemias, and erythroleukemias. There is also acute megakaryoblastic leukemia, acute promyelocytic leukemia, Multiple Myeloma, lymphoblastic leukemia, hypocellular acute myeloid leukemia, Ph-/BCR- myeloid leukemia, acute basophilic leukemia, and acute myleofibrosis. Chromic leukemias include chronic lymphocytic leukemia(CLL, which exists in a B-cell and a T-cell type), prolymphocytic leukemia(PLL), large granular lymphocytic leukemia (LGLL, which goes under several other names as well), chronic myelogenous leukemia(CML), chronic myelomonocytic leukemia, chronic granulocytic leukemia, chronic neutrophilic leukemia, chronic eosinophilic leukemia, and many others.

C. Carcinomas of the Liver include Hepatocellular carcinoma, Combined hepatocellular cholangiocarcinoma, Cholangiocarcinoma (intrahepatic), Bile duct cystadenocarcinoma and Undifferentiated carcinoma of the liver. There are also two types of liver hemangioma: cavernous and hemangioendothelioma.

D. The main types of lung and pleural cancer are small cell (i.e. oat cell, including combined oat cell), adenocarcinoma (Bronchioloalveolar carcinomas (Nonmucinous, Mucinous, and Mixed mucinous and nonmucinous or indeterminate cell type), Acinar, Papillary carcinoma, Solid adenocarcinoma with mucin, Adenocarcinoma with mixed subtypes, Well-differentiated fetal adenocarcinoma, Mucinous (colloid) adenocarcinoma, Mucinous cystadenocarcinoma, Signet ring adenocarcinoma, and Clear cell adenocarcinoma), squamous cell (Papillary, Clear cell, Small cell and Basaloid), mesothelioma (including epithelioid, sarcomatoid, desmoplastic and biphasic) and Large Cell Carcinoma (which include Large-cell neuroendocrine carcinoma, Combined large-cell neuroendocrine carcinoma, Basaloid carcinoma, Clear cell carcinoma Lymphoepithelioma-like carcinoma, and Large-cell carcinoma with rhabdoid phenotype). In addition there are also the carcinomas with pleomorphic, sarcomatoid or sarcomatous elements, including Carcinomas with spindle and/or giant cells, Spindle cell carcinoma, Carcinosarcoma and Pulmonary blastoma. The non-small cell lung carcinomas also include Adenosquamous carcinoma, the Carcinoid tumor (both typical Carcinoid and atypical Carcinoid) as well as carcinomas of salivary-gland type, including mucoepidermoid carcinoma and adenoid cystic carcinoma. There are some soft tissue tumors including localized fibrous tumor (formerly called benign fibrous mesothelioma); epithelioid haemangioendothelioma; pleuropulmonary blastoma; chondroma; calcifying fibrous pseudotumor of the visceral pleura); congenital peribronchial myofibroblastic tumors, diffuse pulmonary lymphangiomyomatosis and desmoplastic round cell tumor. There are assorted bronchial adenomas (eg, adenoid cystic carcinomas, mucoepidermoid carcinomas, mucous gland adenomas, and oncocytomatous bronchial mucous gland adenoma) as well as other adenomas, including papillary adenoma. There

are some papillomas, including squamous cell papilloma and glandular papilloma. There is also malignant melanoma of the lung, Hamartoma, cylindroma (cylindroadenoma), some germ cell tumors, thymoma and sclerosing haemangioma and many others as well.

E. Thyroid cancer comes in four forms: papillary thyroid cancer, follicular thyroid cancer, anaplastic thyroid cancer, and medullary thyroid cancer.

F. Carcinomas of the skin are the Basal cell carcinomas (BCC), including Superficial BCC, Nodular BCC (solid, adenoid cystic), Infiltrating BCC, Sclerosing BCC (desmoplastic, morpheic) , Fibroepithelial BCC, BCC with adnexal differentiation, Follicular BCC, Eccrine BCC, Basosquamous carcinoma, Keratotic BCC, Pigmented BCC, BCC in basal cell nevus syndrome, Micronodular BCC. Another important family is the Squamous cell carcinomas (SCC) which include Spindle cell (sarcomatoid) SCC, Acantholytic SCC, Verrucous SCC, SCC with horn formation, and Lymphoepithelial SCC, along with less well classified SCCs such as Papillary SCC, Clear cell SCC, Small cell SCC, Posttraumatic (e.g., Marjolin ulcer) and Metaplastic (carcinosarcomatous) SCC. Another family is the Eccrine carcinomas including Sclerosing sweat duct carcinoma (syringomatous carcinoma, microcystic adnexal carcinoma), Malignant mixed tumor of the skin (malignant chondroid syringoma), Porocarcinoma, Malignant nodular hidradenoma, Malignant eccrine spiradenoma, Mucinous eccrine carcinoma, Adenoid cystic eccrine carcinoma, and Aggressive digital papillary adenoma/adenocarcinoma. Other carcinomas of the skin include Epidermal carcinomas, Paget disease, Mammary Paget disease, Extramammary Paget disease Adnexal carcinomas, Apocrine carcinoma, Sebaceous carcinoma, Tricholemmocarcinoma and Malignant pilomatricoma (matrical carcinoma).

G. There are many types of colon cancers, and this category is rather diverse. Most are adenocarcinomas, either of the mucinous (colloid) type or the signet ring type. Less common colon cancers include squamous cell, neuroendocrine carcinomas, carcinomas of the scirrhous type, lymphomas, melanomas (which can be primary or metastatic), sarcomas (including fibrosarcomas and Leiomyosarcomas), and Carcinoid tumors.

H. Renal carcinomas include papillary renal cell carcinoma, conventional-type (clear cell) renal carcinoma, chromophobe renal carcinoma, collecting duct carcinoma, and some unclassified cancinomas. Other kidney cancers include Transitional Cell Carcinoma, Wilms Tumors, and Renal Sarcomas.

I. Carcinomas of the prostate are usually adenocarcinomas, but others include small cell carcinoma, mucinous carcinoma, prostatic ductal carcinoma, squamous cell carcinoma of the prostate, basal cell carcinoma, signet-ring cell carcinomas and others.

J. Penile carcinoma is usually a squamous cell carcinoma, but there is also Penile clear cell carcinoma and Sarcomatoid carcinoma.

K. The carcinomas of the extrahepatic bile ducts are of numerous types, including carcinoma in situ, Adenocarcinoma, Papillary adenocarcinoma, Adenocarcinoma (intestinal-type), Mucinous adenocarcinoma, Clear cell adenocarcinoma, Signet ring cell carcinoma, Adenosquamous carcinoma, Squamous cell carcinoma, Small cell carcinoma (oat cell carcinoma) and undifferentiated carcinoma of the extrahepatic bile ducts.

L. Breast cancers come in great variety. The most important category of breast cancers is the ductal cancers. These come in a wide variety of types. Presently, these are divided into the following categories: Intraductal (in situ); Invasive with predominant intraductal component; Invasive, NOS; Comedo; Inflammatory (IBC); Medullary with lymphocytic

infiltrate; Mucinous Carcinoma (colloid carcinoma); Papillary carcinoma; Scirrhous; Tubular; and Other. Another category is the Lobular breast cancers, which can be in situ, Invasive with predominant in situ component, and Invasive. There is Paget's disease of the Nipple, which can be also with intraductal carcinoma or with invasive ductal carcinoma. There is Adenomyoepithelioma , a dimorphic tumor characterized by the presence of both epithelial and myoepithelial cells. There is breast angiolipoma and spindle cell lipoma of the breast. There is lymphoma of the breast (which exists in both Non-Hodgkin's lymphoma of the breast and Hodgkin's disease of the breast forms). There are some sarcomas, including giant cell sarcoma of the breast, leiomyosarcoma of the breast, Angiosarcoma of the breast, cystosarcoma phylloides, and liposarcoma of the breast. There are carcinoid tumors which can be primary carcinoid tumors of the breast, or can arise from from nonmammary sources. There are breast salivary gland-like tumors, including acinic cell carcinoma (AcCC), oncocytic carcinoma (Mammary epithelial oncocytoma), and mucoepidermoid carcinoma (MEC). Other rare carcinomas include Spindle cell carcinoma of the breast (SpCC), Squamous cell carcinoma of the breast, Secretory Carcinoma of the Breast (Juvenile secretory carcinoma), Metaplastic carcinoma of the breast (a heterogeneous group of invasive breast cancers including types with squamous differentiation and those with heterologous elements), Invasive Micropapillary Carcinoma of the Breast, Adenoid cystic carcinoma of the breast, cribriform carcinoma, Myofibroblastoma of the Breast (Benign spindle stromal tumor of the breast) and glycogen-rich clear cell carcinoma of the breast. There are numerous other rare breast cancers, including for example Fibromatosis of the breast (extra-abdominal desmoid), Angiomatosis of the Breast, and mammary hamartoma. There are also nonmammary tumors, primarily

adenocarcinomas, that can metastasize to the breast including bronchogenic carcinomas, malignant melanomas (primary and secondary), rhabdomyosarcomas, malignant mesotheliomas, thyroid carcinomas, renal cell carcinomas, malignant lymphomas, and gastrointestinal carcinomas (including those from the stomach, pancreas, esophagus, and colon).

M. Ovarian cancers are a heterogeneous group of tumors. The most important are the epithelial tumors. These are themselves fairly diverse, the categories being Serous cystomas (Serous benign cystadenomas, Serous cystadenomas with proliferating activity of the epithelial cells and nuclear abnormalities but with no infiltrative destructive growth and Serous cystadenocarcinomas); Mucinous cystomas (divided the same three ways); Clear cell tumors (mesonephroid tumors, again divided the same way), Endometrioid tumors (similar to adenocarcinomas in the endometrium: Endometrioid benign cysts, Endometrioid tumors with proliferating activity of the epithelial cells and Endometrioid adenocarcinomas), mixed mesodermal (now considered to be carcinomas with areas of sarcomatous differentiation), clear cell, transitional cell, and mixed epithelial. Second, there are the Granulosa-Stromal Cell Tumors. These include the Granulosa cell tumor (which exists in juvenile and adult forms) and the tumors in the thecoma-fibroma group. This includes thecoma-fibroma group typical thecoma and luteinized thecoma or "stromal Leydig cell tumor". This also includes fibroma, cellular fibroma, fibrosarcoma, stromal tumor with minor sex cord elements, sclerosing stromal tumor, signet ring cell stromal tumor and others. Third, there are the Sertoli-Leydig Cell Tumors and Androblastomas. These include the Sertoli cell tumor (tubular androblastoma), Sertoli-Leydig cell tumor , a poorly differentiated sarcomatoid, tumor and a Retiform tumor. Fourth, there are some

miscellaneous Sex Cord Stromal Tumors, including Gynandroblastoma of the ovary (composed of sex cord and stromal cells of both ovarian and testicular types), Sex Cord Tumor with Annular Tubules, Stromal luteoma, and Leydig cell tumor)which comes in hilus and non-hilar types). Fifth, there are an assortment of Germ Cell Tumors. These include Dysgerminoma; Yolk Sac Tumors (Endodermal Sinus Tumor, and Polyvesicular vitelline tumor, Hepatoid and others); Embryonal Carcinoma; Polyembryoma; Choriocarcinoma and a wide variety of Teratomas. These tetromas include immature, cystic (dermoid cyst), retiform (homunculus), and Monodermal, including struma ovarii, carcinoid (insular and trabecular), struma carcinoid, mucinous carcinoid, neuroectodermal tumors, sebaceous tumors and others. Finally, there are an assortment of other tumors which do not fit into the above categories. There is Gonadoblastoma and Tumors of Rete Ovarii (which c an be Adenomatoid tumor or a Mesothelioma). There are some tumors of Uncertain Origin, including Small cell carcinoma, tumors of probable Wolffian origin, a Hepatoid carcinoma and Oncocytoma. There are some Soft Tissue Tumors not Specific to Ovary, and there are assorted malignant Lymphomas and Leukemias which land up in the ovaries.

N. Cervical cancers. There are many different categories and sub-categories of cervical cancers. The majority of cervical cancers are Squamous Cell Carcinomas. These come in numerous types: large cell nonkeratinizing type; large cell keratinizing type; Basaloid; Verrucous; Warty; Papillary; Lymphoepithelioma-like; and Squamotransitional, Early invasive (microinvasive) squamous cell carcinoma; Squamous intraepithelial neoplasia (including Cervical intraepithelial neoplasia and Squamous cell carcinoma in situ). There are also a variety of Adenocarcinomas, the most important of which are the Mucinous

adenocarcinoma, which include the Endocervical, Intestinal, signet-ring cell, minimal deviation, and Villoglandular. There is also Endometrioid adenocarcinoma, clear cell adenocarcinoma, serous adenocarcinoma, Mesonephric adenocarcinoma, Early invasive adenocarcinoma, and Adenocarcinoma in situ. In addition, there are neuroendocrine carcinomas, divided into Small Cell, large cell, classical carcinoid and atypical carcinoid. Other epithelial tumors include Adenosquamous carcinoma, mixed Adenosquamous Carcinomas, which can be either well-differentiated or poorly differentiated, the latter including glassy cell carcinoma, adenoid cystic carcinoma, adenoid basal carcinoma and Undifferentiated carcinoma. There are also some mixed carcinoma with signet-ring cells, and other types of other poorly differentiated mixed carcinomas. This group includes tumors sometimes called apudomas or argyrophil cell carcinomas. There are also an assortment of Mesenchymal tumors of the cervix, including Leiomyosarcoma; Endometrioid stromal sarcoma, low grade; Undifferentiated endocervical sarcoma; Sarcoma botryoides; Alveolar soft part sarcoma, Angiosarcoma of the cervix, Malignant peripheral nerve sheath tumor of the cervix; Cervical leiomyoma; and Rhabdomyoma of the cervix. There are also some mixed epithelial and mesenchymal tumors, including Carcinosarcoma (malignant müllerian mixed tumor), Adenosarcoma, Wilms tumor, typical and atypical Polypoid Adenomyoma, and Papillary adenofibroma of the cervix. There are also Melanocytic tumors, including primary malignant melanoma of the cervix and Blue naevus of the cervix. There are also germ cell type tumors, including Yolk sac tumor, Dermoid cyst, and Mature cystic teratoma of the cervix. There is also primary choriocarcinoma of the cervix, which does not fit well into any category. There are also cancers secondary to the cervix, which have spread from elsewhere.

O. Bladder cancers. Most cases of bladder cancers are transitional cell (urothelial) carcinoma, which includes non-invasive papillary urothelial carcinoma, Flat urothelial carcinoma in situ (CIS), Superficially invasive urothelial carcinoma, and muscle invasive tumors. Adenocarcinomas of the bladder include Primary Adenocarcinoma (urachal and non-urachal), Prostatic adenocarcinoma, Gastro-intestinal adenocarcinomas and Clear cell carcinoma. Squamous cell carcinomas include Verrucous carcinomas, and a secondary squamous cell carcinoma of the bladder, from the cervix. Small cell carcinomas include Primary small cell carcinoma of the bladder and the secondary small cell carcinoma ('reserve cell carcinoma') of the lung. Lymphomas include the primary lymphomas (Low grade B-cell lymphoma of MALT type, High grade B-cell lymphoma, and T-cell lymphoma), as well as secondary lymphomas, including mantle cell lymphomas. Melanomas include Primary Malignant melanoma of the bladder, and secondary ones. The sarcomas of the Bladder are Leiomyosarcoma, Osteosarcoma and Rhabdomyosarcoma. There is also a primary primitive neuroectodermal tumour (PNET) of the bladder, Paraganglioma (which can metastasize), Nephrogenic adenoma, Metastatic renal cell carcinoma of the bladder, and both primary and secondary (from the uterus) Choriocarcinoma of the bladder.

P. Cancers of the Vulva are mostly Squamous carcinoma, but these also include Melanoma, Bartholin's Adenocarcinoma, Basal Cell carcinoma and some Sarcomas.

Q. Vaginal cancers are primarily Squamous Carcinoma, but some are Adenocarcinoma, Melanoma of the vagina; Sarcoma of the vagina, Bowen's disease and Germ Cell Tumors.

R. The most important of the cancers of the uterus are the Endometrial Carcinomas. The great majority of these are Endometrioid; others include Uterine Papillary Serous Tumor

(UPST), Clear Cell Carcinoma, Mucinous and Squamous. Uterine Sarcomas include Smooth Muscle Tumors include leiomyoblastoma, clear cell leiomyoma, epithelioid leiomyoma, plexiform tumorlet, Intravenous leiomyomatosis, Benign metastasizing leiomyoma, Leiomyomatosis peritonealis disseminate and Leiomyosarcoma (LMS). Endometrial Tumors include Endometrial stromal nodule, Endolymphatic stromal myosis, (ESM) and Endometrial stromal sarcoma (ESS). There are the mixed tumors Müllerian adenosarcoma and Malignant mixed mesodermal tumors (MMMT). Other sarcomas are Rhabdosarcoma, Osteosarcoma, Chondrosarcoma nad Hemangiopericytoma. There are also uterine cancers which do not come from uterine cells themselves, but start in the tissue that begins to develop immediately after conception: Persistent gestational trophoblastic disease, choriocarcinoma and placental site trophoblastic tumors (PSTT).

S. A hyperproliferative disorder, listed in e.g. in claims 3 and 12 , beyond cancers themselves, is anything that causes any abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue, all of which arise from lack of proper control of cell growth. It can be benign or malignant. Thus, such a term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, and polyps. In addition, it embraces various non-cancerous proliferative disorders such as certain types of restenosis, vascular smooth muscle proliferation associated with atherosclerosis, glomerular nephritis, pulmonary fibrosis, clonal proliferative disorders including the various Myelodysplastic Syndromes (the assorted Refractory Anemias, Ph-Chromosome-Negative Chronic Myelocytic Leukemia, Chronic Myelomonocytic Leukemia

and Agnogenic Myeloid Metaplasia) and the Myeloproliferative Disorders (Chronic myelogenous leukaemia, which exists in adult and juvenile forms; Polycythemia vera;. Agnogenic myeloid metaplasia and Essential thrombocythemia). It includes certain types of abnormal wound healings. It covers numerous types of abnormal angiogenisis e.g. in certain eye diseases (such as neovascular glaucoma, diabetic retinopathy, retinopathy of prematurity, (retrolental fibroplasias), and age-related and certain other types of macular degeneration), Rosacea, some neurodegenerations, respiratory distress in the premature infant, some problems in embryonic development, and atherosclerosis. It includes the myeloproliferative disorders (such as primary polycythemia, primary (essential) thrombocythemia, chronic myelogenous leukemia and myleofibrosis). Also included are numerous Plasma cell dyscrasias, such as Multiple myeloma, Smouldering Myeloma, monoclonal gammopathy of unknown significance (MGUS), solitary plasmacytoma of bone (SPB), asymptomatic myeloma, Waldenström's macroglobulinemia, Solitary extramedullary plasmacytoma, Primary Amyloidosis, POEMS syndrome, and the three heavy-chain diseases). It also includes an assortment of skin disorders, such as psoriasis, atopic dermatitis, allergic contact dermatitis, epidermolytic hyperkeratosis, palmoplantar Pustulosis, lichenified eczema, seborrhoeic dermatitis and the keratinization disorders (including assorted ichthyoses, keratosis pilaris, keratosis follicularis, tylosis, "knuckle pads", corns, assorted callosities, and numerous keratinization disorders found in dogs and cats). Also included are LAM (Lymphangioleiomyomatosis, a smooth muscle proliferative disorder of the lungs) rheumatoid arthritis and even Alzheimer's Disease. It covers most inflammatory and autoimmune disorders. Indeed, almost anything that the body grows ---

skin, blood cells, nerves, plasma, muscles, the vascular network, can grow too fast, or in a manner too undifferentiated.

T. The "autoimmune diseases" (see claim 13) are processes which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There are dozens of such diseases, which have fundamentally different mechanisms and different underlying causes. Known autoimmune disorders, or disorders generally considered to be autoimmune include Polymyositis, Scleroderma, Osteosclerosis, Meniere's disease, Idiopathic neutropenia, Idiopathic thrombocytopenic purpura, Autoimmune hemolytic anemia, Premature ovarian failure, Idiopathic hypoparathyroidism, primary biliary cirrhosis, Pemphigus, multiple sclerosis, autoimmune uveitis, rheumatoid arthritis, Addison's disease, thyroiditis, atrophic gastritis, myasthenia gravis, idiopathic thrombocytopenic purpura, hemolytic anemia, systemic lupus erythematosus, Wegener's granulomatosis, polyarteritisnodosa, erythema nodosum leprosum, Guillain-Barré syndrome (GBS), allergic encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss (IPBSNHL), aplastic anemia, pure red cell anemia, polychondritis, scleroderma, Stevens-Johnson syndrome, idiopathic sprue, lichen planus, Crohn's disease, Graves ophthalmopathy, sarcoidosis, primary biliary cirrhosis, type I diabetes, autoimmune optic neuritis, uveitis posterior, or interstitial lung fibrosis, alopecia, Sjogren's Syndrome, Goodpasture Syndrome, inflammatory bowel disease, Essential Mixed Cryoglobulinemia, Behçet's Syndrome, Chronic Inflammatory Polyneuritis (CIPD), CREST Syndrome, Antiphospholipid Syndrome, Relapsing Polychondritis (systemic chondromalacia or von

Meyenburg disease), Retroperitoneal Fibrosis, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX), Autoimmune Atherosclerosis and many more.

U. Restenosis, or recurrent stenosis, listed in claim 13, is an extremely general term. Stenosis is the narrowing of any canal, orifice, valve, duct, tube (such as trachea), opening, etc. in the body. These can arise from obstructive lesions, deposits of granulations, organ hypertrophy, etc. There is no such thing as being able to treat such widely diverse problems which arise from different and unrelated sources.

The earlier traverse focused on the "renarrowing of a coronary artery after angioplasty or stenting". The claim is not so limited. Narrowing can occur from deposits (of any sort) and do not necessarily have anything to do with uncontrolled cell growth, or angiogenesis. Of course, applicants have not shown that their compounds can control angiogenesis.

V. Prevention of apoptosis. There is no "master switch" for apoptosis. Indeed, there are 3 independent mechanisms by which a cell commits suicide by apoptosis.

1.In the intrinsic (or mitochondrial) pathway, apoptosis is triggered by internal signals. The protein Bcl-2 , by a poorly understood mechanism, reacts to

Internal damage to the cell, and activates a related protein, Bax, which perforates in the outer mitochondrial membrane, causing cytochrome c to leak out.

The released cytochrome c binds to the protein Apaf-1 , which, using ATP,

aggregates to form apoptosomes. The apoptosomes bind to and activate caspase-9. Caspase-9 cleaves and thereby activates other caspases, notably caspase-3 and -7. These in turn create an expanding cascade of proteolytic activity resulting in digestion of structural

proteins in the cytoplasm, degradation of chromosomal DNA, and ultimately phagocytosis of the cell.

2. In the extrinsic or death receptor pathway, apoptosis is triggered by external signals: By an assortment of mechanisms, not all of which are understood, external sources, e.g. cytotoxic T cells, trigger the production of the death activators FasL and a-TNF respectively. These transmits a signal to the cytoplasm that leads to activation of caspase 8, which then initiates a cascade of capsase activation leading to phagocytosis of the cell.

3. A Third pathway does not involve capsases at all. When the cell receives a signal (the full nature of these signals not being understood), the protein AIF is released from the intermembrane space of mitochondria and it migrates into the nucleus. There it binds to DNA, which triggers the destruction of the DNA and cell death. This pathway exists in neurons, but it is not clear what other cells it may also exist in.

The above is an extremely simplified picture; for example processes of signal amplification, exactly how and what capsase 8 activates, the role of p53 activating Bcl-2 and Bax, the roles of the PIG1-PIG13 genes in the process, and the function played by JNK activation are all complex matters. It appears that factors such as eIF4E, splicing factors such as SMN, FAIM, TLE1, AAC-11, fortilin (TPT1), prothymosin-alpha, eIF4E, gelsolin, and DFF tend to inhibit apoptosis, and factors such as the ALG family (e.g. ALG2, ALG3, STM-2), the NADE family (e.g. NADE, BEX, NGFRAP1), CIDE-3, Smac DIABLO, DAXX, CAD, IGFBP-3, STAG1, FLJ21908, TSAP6, HtrA2, PSAP, glycodelin A(PP14), SPARC, NRAGE, and IGFBP-3 promote apoptosis, and there are still others whose role is unclear. There are in fact dozens of biological entities that have been identified as apoptosis factors,

and more are discovered each year. In most cases, little is known how these operate and are regulated, which makes the apoptosis system as a whole substantially unpredictable.
W. Claim 21 is drawn to protecting neuronal cells from antineoplastic agents. This is an odd utility, since these compounds are themselves asserted to be antineoplastic agents. Thus these compounds are asserted to protect nerve cells (of which there are many different types) from these very compounds, which makes no sense at all.

The earlier traverse on this issue was unpersuasive. Applicants asserted, without evidence that "One of ordinary skill in the art ...would have no difficulty understanding in which situations to beneficially apply the present invention." How will this be done? Applicants have simply not addressed the central paradox that these compounds are supposed to protects cells from, in essence, themselves. Just assaying that the compounds "arrest mitotic cell division" doesn't address the point.

Finally, it must be noted that "treatment" in this case includes prevention (prophylaxis) . The specification refers to "prophylactic treatment of a patient at risk of developing a hyperproliferative disease, such as a neoplastic or non-neoplastic, disease comprising administering a prophylactically effective antineoplastic amount of a compound of the formula. A patient at risk of developing a neoplastic disease refers to a patient who ... has ... risk factors associated with the development of neoplastic disease states." It should be noted that the vast majority of adults have at least one risk factor (which the specification gives as examples "genetic predisposition to neoplasms, had or currently have neoplasms, exposure of carcinogenic agents, diet, age") for cancer. Thus, the claims embrace the prevention of cancer and other hyperproliferative disorders.

Earlier, applicants had said, "administration can be accomplished without undue experimentation." Yes, the administration of any drug for any disease can be done without undue experimentation; one of ordinary skill in the art know how to administer a medicinal, but the claims call for the treatment of the disease, and not just the administration of a medicine. Applicants had also made a vague reference to the Sherr and Roberts (1999) publication. It is not clear precisely what this has to do with scope of diseases. The reference, in fact, does not directly discuss the use of pharmaceuticals to treat disease. The reference does have a heavy emphasis on the Kip/Cip family of proteins. These are listed briefly in the background part of the specification, but there is no specific mention that the claimed compounds inhibit members of this family.

(2) The nature of the invention and predictability in the art: With specific reference to cancer, *Ex parte Kranz*, 19 USPQ2d 1216, 1219 notes the "general unpredictability of the field [of] ...anti-cancer treatment." More generally, the invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The traverse is unpersuasive. *In re Fisher* is not considered to be "outdated caselaw". It is cited in MPEP 2164.03; and was cited in In re Wright, 27 USPQ2d 1510 (Fed. Cir. 1993) and *Ex parte Varshavsky*, 63 USPQ2d 1486 (2001). The fact that the CCPA was "dismantled" is of no legal significance; its successor Court adopted its decisions as precedent.

(3) Direction or Guidance: That provided is very limited. The dosage range information provided on page 44 is a range of 0.02-1 mg/kg/day, but this dosage range is of little value because it is completely generic. That is, it is the same dosage for all disorders listed in the specification, from asthma to type-1 diabetes to cancer , which is a very substantial range of disorders. In terms of specific disorders, there are vast pages of disorders listed, especially on pages 7-15 and 21-22. Applicants reply that "dosage determination is very routine". This is not true in certain areas, and cancer is certainly one of them. Many promising anti-cancer drugs have foundered because of an inability to find a dosage regimen that actually works.

In response, applicants earlier argued, "Further, the citation of experimentation of drugs that foundered is evidence that such experimentation is in fact routine, not undue." This is illogical. As the examiner pointed out, many promising anti-cancer drugs have foundered because those of one skilled in the art were unable to find a dosage that actually works. This indicates that it is not a matter of routine experimentation to go from promising in vitro (or animal) experiments to human success. The dosage in the specification, which is the same regardless of whether one is speaking of asthma or cancer, is thus of no real value because it is completely generic.

Applicants now argue that "Applicants believe that the anti-cancer drags, in question may have foundered in the Food and Drug approval process because of a narrow balance between safety and efficacy." Safety is not directly the issue here. The question is the known difficulty of finding a dosage or dosage regimen for anti-cancer drugs which is actually effective. Therefore, there is a greater need of guidance in the realm of dosage for anti-cancer drugs than for e.g. drugs for bacterial infections. Therefore, the fact that the

same dosage is given for a huge variety of largely unrelated disorders, from cancer to Alzheimer's Disease to asthma, means that it is of little value.

(4) State of the Prior Art: The claimed compounds are piperidinyl-amino purines, with a particular substitution pattern at several positions. So far as the examiner is aware , piperidinyl-amino purines have not been successfully used as anticancer agents or for any other utility listed in the specification.

Applicants argued previously that "merely because similar compounds may not have successfully achieved any arbitrary task....." this is not an "arbitrary task" that the examiner refers to; it is the specific utility claimed. The fact that such compounds have not been successfully used means that applicants cannot "piggy-back" on the success of those compounds, e.g. in terms of the dosages or medical regimen. Therefore, more experimentation would be needed than in a case where similar compounds were already established to work. In this regard, applicants cited the Knockaert reference, but it is difficult to see how this reference can be evidence of enablement. A simple listing of "The potential applications of cyclin dependent kinase (CDK) inhibitors" as appears in the Figure 3 that applicants point to is hardly the same thing as establishing enablement, especially since none of the compounds mentioned in the reference had been established as actually being effective for the treatment of a disease. Indeed, the concluding remarks state ""However, their cellular targets remain to be identified", which is certainly evidence of low skill in this art. Further, and very importantly, it is clear that applicants compounds are quite atypical. The paper says in its concluding remarks, "Most CDK inhibitors have antiproliferative properties associated with apoptosis inducing activity and display anti-

tumoural activity." However, applicants compounds have the opposite property. These compounds are said to prevent apoptosis (see claim 15). Therefore, since in those compounds, the "antiproliferative properties" are "associated with apoptosis inducing activity", and since applicants compounds have the opposite property, one cannot rely on any of this knowledge at all, and to the extent that one could rely, the paper is an argument against enablement, since it teaches that the antiproliferative properties arise from inducing apoptosis, and applicants compounds prevent apoptosis generally.

Applicants now argue: "Someone has to pioneer a field. The present Applicants have made pioneering contributions to this art recognizing benefits of inhibiting cyclin dependent kinases and providing novel compounds that inhibit them.. While perhaps Applicants cannot piggy-back on past successes of others..." Applicants may well have a pioneering invention. But an inability to piggy-back on past successes of others means that there is more work to be done here, as one cannot rely on the work done by other with similar structure and having similar pharmacological effects. This thus weighs in toward there being more experimentation needed.

(5) Working Examples: There are no working examples to the treatment of any actual disease. Table 2 shows inhibition of three CDKs, which cannot be said to be representative of the class as a whole. Table 3 lists test results in 3-5 cell lines, and example 4 gives results in xenografts on two cell lines, one an acute leukemia, and one for a prostate cancer. No testing for autoimmune diseases or restenosis appears.

The traverse is unpersuasive. Applicants state, "However, disease models are effectively inhibited from cell culture experiments." The examiner does not understand this sentence. What does it means that a disease model is inhibited?

Next applicants state, "Claims specify three CDKs. Inhibition of these is demonstrated in the application to effect inhibition of cyclin dependent kinases... The Examiner has provided not rationale, why such should not be the case." This appears to be referring to claims 22-23, but these claims are not under rejection.

Next, applicants state, "Methotrexate is a compound with a similar but not identical mechanism." This point is not agreed with at all..Methotrexate acts primarily as a folate antagonist; applicants' compounds are not disclosed to be folate antagonists. MTX is well known to induce apoptosis in e.g. activated T cells. Applicants compounds are said to suppress apoptosis. Applicants compounds act, by inhibiting three CDKs and their complexes. So far as the examiner is aware, MTX is not a CDK inhibitor. MTX has a cytotoxic mode of action; applicants compounds, so far as can be determined from the specification, do not operate via a cytotoxic mode of action. Thus, any notion that these compounds and MTX have a "similar" mechanism of action is without scientific basis.

(6) Skill of those in the art: The prior art knows that there never has been a compound capable of treating cancer generally. "The cancer therapy art remains highly unpredictable, and no example exists for efficacy of a single product against tumors generally." (<http://www.uspto.gov/web/offices/pac/dapp/1pecba.htm#7> ENABLEMENT DECISION TREE, Example F, situation 1) There are compounds that treat a modest range of cancers, but no one has ever been able to figure out how to get a compound to be effective

against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. This is because it is now understood that there is no "master switch" for cancers generally; cancers arise from a bewildering variety of differing mechanisms. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (an estimated at least 20% are of viral origin e.g. EBV, HHV-8, HTLV-1 and other retroviruses), exposure to chemicals such as tobacco tars, genetic disorders (e.g. Tuberous Sclerosis), ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Cancers that affect just a certain type of structure can be quite varied. Fibromas for example include Infantile myofibromatosis, Fibrous hamartoma of infancy. Juvenile hyaline fibromatoses. Infantile digital fibromatoses. Calcifying aponeurotic fibromas. Giant cell fibroblastoma. Ovarian fibroma, Dermatofibroma, myofibroma, myofibromatosis, desmoplastic fibroma, neurofibroma, peripheral odontogenic fibroma, peripheral ossifying fibroma, giant cell fibroma, Chondromyxoid Fibroma, Oral Neurofibroma, Juvenile aponeurotic fibroma (JAF), aggressive infantile fibromatosis (AIF), omental fibroma, Perifollicular fibroma, ameloblastic fibroma, Premalignant Fibroepithelial Tumor (Pinkus Tumor), Periungual fibroma (Koenen tumor), desmoid tumor, tracheal fibroma and many others. Since it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. The skill thus depends on the particular cancer involved. There are a few cancers

where the skill level is high and there are multiple successful chemotherapeutic treatments. One skilled in the art knows that chemotherapy of brain tumors is especially difficult. This is because 1) the blood-brain barrier, which is often intact in parts or all of a brain tumor, will block out many drugs, as it is the purpose of the blood-brain barrier to protect the brain from alien chemicals, and 2) CNS tumors are characterized by marked heterogeneity, which greatly decreases vulnerability to chemotherapy. As a result, many categories of CNS tumors simply have no chemotherapy available. These include, generally, hemangiomas and hemangioblastomas, meningiomas, craniopharyngiomas, acoustic neuromas, pituitary adenomas, optic nerve gliomas, glomus jugulare tumors and chordomas, to name just some. With regard to gliomas, GBM is considered untreatable; no effective agents have emerged for the treatment of GBM, despite 20 years of enrolling patients in clinical trials. It is radiation and surgery which are used for low grade gliomas (e.g. Pilocytic astrocytoma and Diffuse astrocytomas), as no drug has been found effective. There is no drug treatment established as effective for optic nerve gliomas or gangliogliomas. Indeed, very few gliomas of any type are treated with pharmaceuticals; it is one of the categories of cancer that is the least responsive to drugs. Cartilage tumors do not respond to chemotherapy, nor do Cancerous teratomas. Of the thyroid cancers, only one (anaplastic thyroid cancer) can be treated with anticancer agents. The other are treated with radioactivity, surgery, or thyroid suppression hormones. Neuroendocrine tumors of the cervix generally do not respond to chemotherapy. Renal cell carcinoma does not respond to chemotherapy. A number of sarcomas, including Alveolar soft part sarcoma (ASPS), retroperitoneal sarcoma, most liposarcomas (see claim 9), and the assorted chondrosarcomas, are generally considered not to respond to chemotherapy; no

chemotherapeutic agent has been established as effective. Many cerebral metastases, such as those from non-small-cell lung cancer and melanoma, are not chemosensitive and will not respond to chemotherapy. Hepatocellular Carcinoma is, in humans, possibly the most prevalent solid tumor. Despite strenuous efforts over a period of decades, no chemotherapeutic agent has ever been found effective against this cancer.

Applicants' most recent response indicates that they may not be entirely clear on the purpose of the list. The list is there to explicate the scope of the claims. Applicants state, "All the listed diseases share a property of cell hyperproliferation." Correct; that is how the list was constructed. All cancers for example, involve one or more types of hyperproliferation.

Applicants state, "The size of a list the Examiner chooses to put together is no indication of a requirement of a requirement for undue experimentation." This is mistaken. As was noted above, the scope of the claims is one of the factors that must be taken into account when determining whether undue experimentation will be required to enable the claims. The broader the claim, the more that is entailed. This is because there is more that must be enabled. As was stated in In re Wright, 27 USPQ2d 1510, 1513 , "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation'." The larger that this "full scope" is, the more there is which needs to be enabled.

Applicants had earlier pointed to Table 3, which applicants refer to as "a cross-section of cancers. To begin with, five cancers cannot conceivably be a cross-section of cancers generally. Applicants have 2 leukemias, three carcinomas (a lung, breast, prostate), and one adenocarcinoma (colon). There is not one lymphoma, sarcoma, glioma, fibroma,

blastoma, melanoma etc. There is not one test for a non-cancerous hyperproliferative disorder.

In discussing the various cancer categories, applicants on page 12-13 again make the point that each one of these involves hyperproliferation. But the notion that any antiproliferative compound can be made to work against any cancer with no more than routine experimentation is without any scientific basis, even though applicants seem to assert that it is true on its face. There are thousands of compounds which have been established as antiproliferative. Hepatocellular Carcinoma is, as noted above, possibly the most prevalent solid tumor. Yet, there is no phrarmaceutical treatment available for this proliferative disorder. Yet, according to applicants reasoning, there should many --- any known anti-proliferative against should work. The fact that there are so many cancers --- indeed, entire categories of cancers, which cannot be treated with any pharmaceuticals disproves applicants' assumption that simply being an antiproliferative agent means that the compounds can be expected to be effective against cancers.

Applicants argue "many compounds are used in more than one cancer." This is certainly true. But there is a huge gap between a compound which can treat several cancers, and one which will treat cancer generally. Applicants state, "Just because no compound is deemed "best for all cancers does not mean that general applicability does not exist." Agreed, but that is not the examiner's argument. The examiner states that there is no compound which is effective against cancers generally, regardless of whether it is best or 10th best. If applicants disagree, they are invited to name the anti-cancer drug they are referring to.

With regard to smooth muscle proliferative disorders, the skill level is very low. Janet R. Maurer, Lesson 23, Volume 14–Lymphangioleiomyomatosis http://www.chestnet.org/education/online/pccu/vol14/lesson23.php is cited as the state of the art for LAM. The article states that it is a "disease of unknown cause" and that "two groups: those with sporadic disease and those with TSC-associated disease." It goes on to say that "LAM remains an elusive disease. Do sporadic LAM patients have a genetic link to TSC patients? What triggers the disease? Why the lungs? ... these are still largely unanswered questions". While there is supportive care, treatment methods are very problematic. The article notes, "It is also not clear whether current treatments influence the course of the disease", which is clear evidence of the very low skill level in this art. The essay notes that "No prospective studies assessing any of these therapies have been conducted because the progression/regression of disease is hard to monitor, and the natural course is highly variable." Further, it should be noted that treatment has involved "Hormonal manipulation", e.g. "progesterone, tamoxifen or similar agents, luteinizing hormone-releasing hormone, oophorectomy, and radioablation of the ovaries." This is totally unrelated to the alleged method of action of the claimed compounds.

The page 18 traverse on this point is unpersuasive. The above quotes make it abundantly clear that the skill level is low in this area. It is correct that the treatment method explored so far, the use of hormones (which has not been established as efficacious) is unrelated to applicants method, and indeed, the examiner said that explicitly. The point is that the investigation so far of treatment for the proliferative disorder LAM has involved a totally different approach, so that the skill level for using CDK inhibitors for this is even lower, since the area hasn't, so far as the examiner is aware, even been invenstigated.

More broadly, the low skill level in the art of proliferative disorders (other than cancers) is seen by the fact that many such proliferative disorders are entities of unknown origins. These include Rosai-Dorfman disease (Sinus histiocytosis with massive lymphadenopathy), Benign prostatic hyperplasia (BPH), Kimura disease, Langerhans cell histiocytosis (LCH), Pigmented villonodular synovitis, essential thrombocythemia, Madelung's disease (benign symmetrical lipomatosis), Castleman's disease, Craniomandibular osteopathy, and Pulmonary capillary hemangiomatosis.

Again here, applicants simply assert that all proliferative disorders can be treated without undue experimentation because applicants compounds are antiproliferative agents. But applicants have not come to terms with the fact that, even aside from cancers, that the opposite has proved to be true. Consider Alzheimer's Disease, which is considered a cell proliferative disorder, and which has been extensively studied. Despite a large array of anti-proliferative drugs available, not one has been made to work against Alzheimer's Disease. Or consider idiopathic pulmonary fibrosis, a devastating lung disease of unknown etiology. No antiproliferative drug has been found; indeed, no drug has been firmly established as effective against the disease itself. Where is the antiproliferative drug found effective against tylosis or retrolental fibroplasia? If hyperproliferative disorders generally could be treated with anti-hyperproliferative agents, these disorders would avh plenty of such treatment. The fact of the matter is, hyperproliferative disorders are extremely diverse, and no agent of any kind can treat them generally because their origins are so different (when known).

With regard to autoimmune diseases, there are both chronic and acute, most of which lack satisfactory treatment. As a class, autoimmune diseases are among the most

difficult to treat or even diagnose. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished.

A major difficulty arises from the fact that there are four basic mechanisms underlying autoimmune disease: 1. Antibody mediated diseases: a specific antibody exists targeted against a particular antigen (protein), which leads to its destruction and signs of the disease. Examples are: auto-immune mediated hemolytic anemia, where the target is on the surface of the red blood cell; myasthenia gravis where the target is the acetylcholine receptor in the neuromuscular junction; hypoadrenocorticism (Addison's) where the targets are the cells of the adrenal gland. 2. Immune-complex-mediated diseases: antibodies are produced against proteins in the body. These combine into large molecules that circulate around the body. In systemic lupus erythematosus (SLE) antibodies are formed against several components in the cell's nucleus (hence the anti-nuclear antibody test (ANA) for SLE). Most notably antibodies are made against the body's double stranded DNA, and form circulating soluble complexes of DNA and antibody, which break down in skin causing an increased sensitivity to ultraviolet light and a variety of signs. As the blood is filtered through the kidneys, the complexes are trapped in the glomeruli and blood vessels, causing the kidney to leak protein - glomerulonephritis. They also cause leakage in other blood vessels, and there may be hemorrhaging, as well as accumulating in synovial fluid and causing signs of arthritis and joint pain. Rheumatoid arthritis results from immune complexes (IgM class antibody called rheumatoid factor) against part of the patient's own immune system (part of its IgG molecules). These form complexes that are deposited in the

synovia of the joint spaces causing an inflammatory response, joint swelling, and pain. The collagen and cartilage of the joint breaks down and is eventually replaced by fibrin which fuses the joints - ankylosis. 3. Antibody and T Cell-mediated diseases: T cells are one of two types (the other being B-cells), which mediate immune reactions. Upon exposure to a particular antigen, they become programmed to search for and destroy that particular protein in future. Once a patient has been exposed to an antigen, he will be able to mount a much faster response to it the next time it encounters it. This is the basis of vaccination. Thyroiditis (autoimmune hypothyroidism) seems to be of mixed etiology. Several target antigens have been identified, including thyroglobulin the major hormone made by the thyroid. Auto-antibodies to antigens in the epithelial cells of the thyroid have also been found. The thyroid becomes invaded by large numbers of T and B cells as well as macrophages, which are cells that engulf and destroy other cell types. T cells specifically programmed for thyroglobulin have been identified. Autoimmune disorders can arise from the killer T-cells, from the helper T-cells, or from the regulatory T-cells (e.g. IPEX syndrome). 4. Diseases arising from a deficiency in complement: When an antigen and antibody react they may activate a series of serum enzymes (the complement system) whose end result is either the lysis (breakup) of the antigen molecule or to make it easier for phagocytic cells like the macrophages to destroy it. Patients with deficiencies in enzymes activated early in the complement system develop autoimmune diseases like SLE. Thus, with such differing mechanisms, it is not logical that a treatment for autoimmune diseases generally can be found.

Claim 14 lists the autoimmune disorders, Type 1 diabetes, atherosclerosis and asthma. Such disorders have never been treated successfully with agents that suppress the

immune system, and of course there is no evidence at all that these compounds do in fact suppress the immune system. Moreover, atherosclerosis itself is not per se treatable. Thus, the state the skill of the art in treating these three disorders with immune suppression agents is very low.

The traverse is unpersuasive. Applicants earlier argued that "interfering with immune cell proliferation is one tool for ameliorating symptoms of autoimmune disease" and applicants name glucocorticoids as an example of compounds effective generally. As is noted below in ③, ameliorating symptoms is not the same thing as treating the disorder itself. The use of glucocorticoids to deal with complications (such as serositis, vasculitis, or glomerulonephritis) of autoimmune disorders like SLE does not mean that it is treating the disorder itself. The examiner must also note that applicants have not established that their compounds act as glucocorticoids act.

Applicants also argued that "unifying features such as cellular proliferation are ignored." The term "cellular proliferation" is a very general one, like "protein synthesis" or "cell signaling"; it exists both in normal and abnormal body processes, and it covers a broad range of processes. Most human disease involves proliferation of cells. All infectious disorders, all inflammatory disorders, nearly all skin and bone disorders, and nearly all neonatal disorders, for example, involve proliferation of cells. Shutting down cellular proliferation per se will simply kill the host, since it is essential for normal body processes.

In one only place where applicants did get specific: applicants previously stated, "the fact remains that in B-cell (antibody mediated) autoimmune disease, B-cell proliferation is a component. Thus, inhibiting hyperproliferation of, in this instance, B-cells would have

the effect of at least ameliorating the symptoms of autoimmune disease." This is unpersuasive for the following reasons:

① The examiner cannot locate, in this 183 page specification, even any mention of applicants compounds having any effect at all on B-cells. Applicants note that the specification does not need to teach what one of ordinary skill in the art knows. This is true, but one of ordinary skill in the art knows nothing about these compounds because these compounds are novel.

② Even if true, many types of autoimmune disorders have nothing at all to do with B-cells. Thus, some are mediated by T-cells, some are mediated by antibodies, and some arise from a deficiency in complement system.

③ Even if true, palliation of symptoms is not the same things as treatment of a disorder. Giving pain medicines to people with bone cancer or shingles will ameliorate the symptoms, but its is not treatment of the disorder itself.

Applicants now respond by saying, "The Office .Action bases this rejection in part on the omission in the specification of B-cell involvement in antibody production...Does the Examiner mean to indicate that B-cells do not make antibodies or that B-Cells do not proliferate, or that they proliferate by a cell cycle independent mechanism? Applicants are not required to list all truths in a patent application."

None of these things (except the last sentence) are true. The rejection is based on the grounds set forth. In rebutting this, applicants had said that "the fact remains that in B-cell (antibody mediated) autoimmune disease, B-cell proliferation is a component. Thus, inhibiting hyperproliferation of, in this instance, B-cells would have the effect of at least

ameliorating the symptoms of autoimmune disease." The examiner did not find this argument persuasive, and the examiner set forth three reasons why this rebuttal was not found persuasive. Those are the reasons with the circled points. For example, applicants argument focused on one type of autoimmune disease, viz., B-cell (antibody mediated) autoimmune disease. The examiner pointed out that that this huge specification had no mention of their compounds having this specific effect, or indeed any effect, on B-cells. It is correct that the specification is not obliged to reveal "all truths", but applicants cannot rely on this specific effect on B-cells if this 183 page specification makes no mention of B-cells.

And as for the "Does the Examiner mean....." sentence, the examiner was not saying any of these choices. The examiner's point under ② was that even if applicants compounds did what applicants (now) say they do with regard to B-cells, many, many autoimmune disorders have zero to do with B-cells.

Applicants now argue that with regard to autoimmune diseases, "Some involve hyperproliferation...To the extent that hyperproliferation is involved, the present invention provides antiproliferative agents and methods to counter the disease." However a) as noted above, such generalizations are not valid and b) the claims are not limited to just the autoimmune disorders which involve hyperproliferation. These cover others as well. Even if one of ordinary skill in the art could determine that a given autoimmune disorder did not involve hyperproliferation --- no easy task, given how mysterious many auto-immune diseases are --- that determination does not make the disease outside the claim, not does it help in enabling the claim.

Applicants also argue on page 17 that methotrexate is of "general benefit" in treating autoimmune diseases. First, while MTX is useful is certain autoimmune disorders,

especially those involving connective tissue, it is certainly not effective generally. For example type 1 diabetes, listed in claim 14 as an autoimmune disease, cannot be treated with MTX, and indeed, people with diabetes are generally told to avoid taking MTX. MTX has never been established as effective for atherosclerosis, also listed in claim 14, and indeed, there is some evidence that MTX is detrimental in patients with established atherosclerosis. Second, as discussed above, MTX has an utterly different mode of action.

On the matter of restenosis, much the same approach is taken, in which applicants appear to concede that restenosis in some cases does not involve hyperproliferation. But again, the claims do not exclude those choices

On the matter of apoptosis, applicants stated previously, "With respect to apoptosis, Applicants respectfully submit that there is no requirement in the claim language that the blocking or augmenting of apoptosis has to be in all cells as could be inferred from the Office Action." However:

a) Where did this "or augmenting" come from? The claims say only "preventing apoptosis", not "augmenting".

b) The claim language is "cells", without limitation, and for that matter, the "apoptosis" is without limitation as well, and thus the claim covers all cells involved with all three types of apoptosis (see discussion above of 3 independent mechanisms of apoptosis). And thus, the terms are understood exactly as written. *Johnson Worldwide Associates Inc. v. Zebco Corp.*, 50 USPQ2d 1607, 1610 states that "modifiers will not be added to broad terms standing alone. See e.g., *Virginia Panel Corp. v. MAC Panel Co.* , 133 F.3d 860, 865-66, 45 USPQ2d 1225, 1229 (Fed. Cir. 1997) (unmodified term "reciprocating" not limited to linear reciprocation); *Bell Communications Research Inc. v. Vitalink* , 55 F.3d at 621-22, 34

USPQ2d at 1821 (unmodified term "associating" not limited to explicit association); *Specialty Composites v. Cabot Corp.* , 845 F.2d 981, 987, 6 USPQ2d 1601, 1606 (Fed. Cir. 1988) (unmodified term "plasticizer" given full range of ordinary and accustomed meaning)."

In addition, applicants stated, " Applicants respectfully submit the Examiner's comments relating to too little apoptosis may find mitigation in slowing proliferation of cells rather than proliferating and then inducing apoptosis." The examiner cannot understand the point being made here. The examiner's reasoning is as follows:

A. Some important autoimmune disorders such as lupus and MS and Sjögren's syndrome are characterized by too little apoptosis.

B. Applicants compounds are disclosed to suppress apoptosis.

C. Therefore, these agents would be expected to make lupus and MS and Sjögren's syndrome worse.

If applicants disagree with this reasoning, applicants are asked to identify which lettered statement they find fault with and explain specifically why.

In their most recent response, applicants do not address this question. Applicants on pages 14-16 cite and discuss three references, but no copies were provided; the references are not of record and hence this argument cannot be considered.

Applicants argue at the bottom of page 17 that "Lack of FDA approval of a compound has never been grounds to invalidate a claim." The examiner has never referred to the fact that applicants compounds have not been approved. The examiner is unaware whether applicants compounds have even been submitted for FDA approval.

(7) The quantity of experimentation needed: Given the fact that historically the development of new cancers drugs has been difficult and time consuming, and especially in view of factors 1, 4, 5 and 6, the quantity of experimentation needed is expected to be great.

Applicants' primary legal argument in the previous response was that inoperatives are of no significance. This is not a valid statement of the law.

It is entirely proper to reject claims which have a significant or substantial inclusion of inoperative embodiments, even if there are also included operative embodiments. This is analogous to the fact that rejections can be made under 102 or 103 even if nearly all of the claim is not rejectable. MPEP 2164.08 states, "The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation'." *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)" (emphasis added).

This principle has been demonstrated many, many times. In *Graver Tank & Mfg. Co. v. Linde Air Products Co.*, 336 U.S. 271, 276-77, 80 USPQ 451, 453 (1949), the Supreme Court affirmed a finding of invalidity of claims drawn to both operative and inoperative embodiments. *In re Buting*, 57 CCPA 777, 418 F.2d 540, 163 USPQ 689, and *In re Harwood*, 55 CCPA 922, 390 F.2d 985, 156 USPQ 673, both sustained rejections of claims encompassing both operative and inoperative applications of a compound. In *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974), method claim 11, encompassing both operative and inoperative compounds was rejected, while narrower claims 12 and 17 were allowed. *In re Cortright*, 49 USPQ2d 1464, 1466 states that claims must be limited to enabled subject matter: "The PTO will make a scope of enablement rejection where the written description enables something within the scope of the claims, but the

claims are not limited to that scope." *Scripps Research Institute v. Nemerson*, 78 USPQ2d 1019 asserts: "A lack of enablement for the full scope of a claim, however, is a legitimate rejection." In *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer Inc.*, 49 USPQ2d 1370, the court held that if the examiner had been told that three of the protecting groups did not work, "the examiner would have been required to disallow those claims of the '011 patent for lack of sufficient evidence or enablement."

A particularly strong statement of this occurs in *In re Cook and Merigold*, 169 USPQ 298, 302, where the court stated, "We see no reason why the Patent Office ... should not "have authority to reject a broad claim merely because it * * * [reads on a significant number of] inoperative species"". Noting that "during the prosecution of patent applications * * * an applicant is still in a position to amend his claims to exclude inoperative subject matter", the Court further stated, "when the examiner sets forth reasonable grounds in support of his conclusion that an applicant's claims read on inoperative subject matter ... it becomes incumbent upon the applicant either to reasonably limit his claims to the approximate area where operativeness has not been challenged or to rebut the examiner's challenge either by the submission of representative evidence ... or by persuasive arguments based on known laws of physics and chemistry." The decision makes one exception, when claims have "inoperative embodiments in the trivial sense that they can and do omit "factors which must be presumed to be within the level of ordinary skill in the art," *In re Skrivan*, 57 CCPA 1201, 427 F.2d 801, 806, 166 USPQ 85, 88 (1970), and therefore read on embodiments in which such factors *may* be included in such a manner as to make the embodiments inoperative. There is nothing wrong with this so long as it would be obvious to one of ordinary skill in the relevant art how to include those factors in such

manner as to make the embodiment operative rather than inoperative". (emphasis in the original). The *Skrivan* situation was one where a "Jepson" type claim did not specifically say that the process had to be done at an operable mixing angle; the Court held that this was "a physical operating condition of an admittedly old process" and hence one of ordinary skill in the art would know how to do the reaction correctly. Such a circumstance clearly does not pertain here.

A particularly extreme form of rejection of claims for inclusion of an inoperative embodiment occurred in *Ex parte Jovanovics*, 211 USPQ 907, where the method of Claim 1 used a genus of only two (2) extremely similar compounds. The data for one of the compounds was deemed persuasive (and a dependent claim for that was allowed); no data was presented for the other, and hence the rejection was affirmed --- even though the claim had only a single inoperative embodiment. Similarly, *In re Rainer*, 153 USPQ 802 found lack of enablement on the basis of a single specification example which did not work.

In general, however, the amount of inoperables must be "significant" or "substantial". *In re Corkill*, 226 USPQ 1005, 1009 states that "Claims which include a substantial measure of inoperatives ... are fairly rejected under 35 U.S.C. §112. *Durel Corp. v. Osram Sylvania Inc.*, 59 USPQ2d 1238, 1244 states, "if Sylvania had shown that a significant percentage of oxide coatings within the scope of the claims were not enabled, that might have been sufficient to prove invalidity." *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 414 states: "[I]f the number of inoperative combinations becomes significant, and in effect, forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid."

The standard for the examiner challenging enablement is one of reasonable doubt. Thus, *In re Langer*, 183 USPQ 288 put the standard as when "there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." (emphasis added). Similarly, "after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility" the burden shifts to the applicant "to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility" *in re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441. The "reason to doubt the objective truth of the statements contained in the written description" standard is set forth in *In re Cortright*, 49 USPQ2d 1464, 1466. In *Fregeau v. Mossinghoff*, 227 USPQ 848, all that was needed was a statement by appellant that the invention "is one about which those of ordinary skill in the flavor chemistry art would be skeptical when first hearing of it". In the context of determining whether sufficient "utility as a drug, medicant, and the like in human therapy" has been alleged, "it is proper for the examiner to ask for substantiating evidence unless one with ordinary skill in the art would accept the allegations as obviously correct." *In re Jolles*, 628 F.2d 1322, 1332, 206 USPQ 885.

Such a standard can readily be met in such cases:

A. As noted above, *Ex parte Busse*, et al., 1 USPQ2d 1908, asserted that a claim drawn to treatment of cancer generally "is sufficiently unusual to justify the examiner's requirement for substantiating evidence."

B. The PTO's own examination guidelines as noted above state, "no example exists for efficacy of a single product against tumors generally". This means that even a single such compound would be without precedent, which is reason to doubt the assertion that an entire genus can accomplish this. The reasons for this lie in the great diversity of cancers.

C. There are in fact substantial numbers of cancers which appear to be resistant to chemotherapy. As noted above, possibly the most widespread solid tumor, Hepatocellular Carcinoma, has no effective chemotherapy, nor does Renal cell carcinoma and other examples listed above. Indeed, the Peckham, ed., Oxford Textbook of Oncology Volume 1 (Oxford University Press, 1995), page 452 reference, referring to chemotherapy sates, "the majority of common cancers to not respond to this treatment". That is, even if applicants' compounds were to magically have the combined properties of ALL known anticancer agents, one would still not expect them to be effective against even a majority of cancers, given the current experience.

In rebuttal, the remarks had stated, "*Wands* is instructive that when even a majority of embodiments are inoperative, the experimentation is presumed to be undue." It is difficult to know what to make of this statement. If experimentation is undue, then enablement is lacking. It is possible that applicants intended the word "not" to appear before "undue." If so, such a statement does not appear in the decision; applicants are asked to provide a direct quote to that effect. At any rate, the decision stated "We conclude that the board's interpretation of the data is erroneous. It is strained and unduly harsh to classify the stored cell lines (each of which was proved to make high-binding antibodies against HBsAg) as failures".

Applicants at the bottom of page 18 of the most recent response discuss the analogy to 102 and 103 rejection, but miss the examiner point. The examiner was not discussing a claim which had many required elements, but rather a genus which embraced many embodiments.. Suppose a genus embraced 1000 species, and a reference disclosed just one.

A 102 rejection could still be made, even though 99.9% of the claim was not rejectable. That was the examiner's only point.

Applicants point to *Atlas Powder*, as saying that the number of "inoperative combinations becomes significant", although of course, the issue of "inoperative combinations" does not arise here. As for the "unduly" in that quote, as the examiner noted, "one considers the following factors to determine whether undue experimentation is required". Factor after factor points toward undue experimentation, including the staggering array of largely unrelated diseases, including many diseases that have resisted all forms of pharmacological therapy, the fact that these compounds are not closely related to other agents established as effective, and the fact that these are drawn to some of the most difficult areas of medicine, cancer and autoimmune disorders.

Applicants on page 19 request that a "utility rejection be made of record". Assuming that a 35 USC 101 rejection is being referred to, none has been made or will be made.

In response to the above legal analysis, applicants state: "Applicants' argument is that inoperative embodiments are tolerated so long as practicing the claimed invention, e.g., finding the next working embodiment does not require undue experimentation. The examiner understands that this is applicants' position, but does not agree. For example, such an assertion is flatly inconsistent with *Ex parte Jovanovics*, 211 USPQ 907, discussed above. There were only two embodiments, and it was exactly determined which was inoperative and which was not. According to applicants' reasoning the claim should have been allowable. Similarly, *In re Corkill*, 226 USPQ 1005, 1009 states that "Claims which include a substantial measure of inoperatives ... are fairly rejected under 35 U.S.C. §112" -- - a flat assertion, without any qualification about "finding the next working embodiment." A

similar unqualified statement appears with *Scripps Research Institute v. Nemerson*, 78 USPQ2d 1019: "A lack of enablement for the full scope of a claim, however, is a legitimate rejection."

Finally, applicants also argue: "The Examiner appears to rely on a per se rule that treatment of cancers and hyperproliferative disorders cannot be considered enabled." That is not the case. If the examiner were arguing that, all of the above detailed analysis would not have been made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-10, 12-16, 18-19, 21-35, 48-49 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6861524. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims here are just generic to the species already patented in the parent case. The method claims are also rejected, because there was no restriction in the parent, and method claims are not patentably distinct form compound claims.

Claim Objections

Claims 9, 49 are objected to because of the following informalities: Claim 9 should have "liposarcoma"; claim 49 should have myelocytic. Appropriate correction is required.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300 for regular communications and (571) 273-8300 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0198.

/Mark L. Berch/
Primary Examiner
Art Unit 1624

5/22/2007